REMARKS

I. Status of the Claims

Claims 1-3, 8-10, and 50-56 are currently under examination on their merits. Claims 4-7, 11-49 have been canceled without disclaimer or prejudice against the prosecution of the claims in future applications. Claims 1 and 10 are amended to further clarify the scope of the invention. New claims 50-56 are added. Support for the claim amendments can be found throughout the specification as originally filed, for example, on page 3, last paragraph to page 4, first paragraph, Examples 17-18, and claim 10 as originally filed. Thus, the amendments do not introduce new matter.

II. Claim Rejection Under 35 U.S.C. §112, First Paragraph, Enablement

Claims 1-3 and 8-10 remain rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to satisfy the enablement requirement. Previously, the Office asserted that the specification, while enabling a method of inhibiting tumor proliferation *in vitro*, does not enable a method of inhibiting tumor proliferation *in vivo*. See page 3 of the Office Action dated June 27, 2007 ("the June 27, 2007 Office Action"). In response, Applicants submitted a Declaration under 37 CFR 1.132 by Dr. I-Ching Wang, in which Dr. Wang testified that the wild type p19ARF 26-44 peptide inhibits tumor cell growth *in vivo* as well as *in vitro*. *See* paragraph 11 of Wang's Declaration dated October 26, 2007 ("the October 26, 2007 Declaration"). While acknowledging the Declaration showed that the peptide of SEQ ID NO:10 inhibited hepatocellular tumor proliferation *in vivo*, the Action nevertheless asserts that the *in vivo* data do not enable the method of inhibiting proliferation of other types of tumor. Applicants respectfully disagree.

An analysis of enablement requires a determination of whether the specification contains sufficient information regarding the subject matter of the claims so as to enable one skilled in the art to make and use the claimed invention, without undue experimentation. MPEP §2164.01. A patent need not teach, and preferably omits, what is well known in the art. MPEP §2154.01. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent, coupled with information known in the art, without undue experimentation. U.S. v. Telectronics, Inc., 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988).

The Office has the burden to establish a *prima facie* case of non-enablement. As stated in the *In re Armbruster*, which is cited in this Action, "[t]he first paragraph of 112 requires nothing more than objective enablement.... [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." 185 USPQ 152, 153 (CCPA 1975) (*citing In re Marzocchi*, 169 USPQ 367 (CCPA 1971)) (emphasis original). The court in *In re Armbruster* made it clear that the Office "must substantiate its rejection for lack of enablement with *reasons*." See 185 USPQ at 153. (emphasis original).

Additionally, Applicants respectfully submit that there is simply no requirement that a specification contain evidence of actual reduction to practice; indeed, filing a patent application is constructive reduction to practice and has sufficed to satisfy the enablement requirements for over a century. *Dolbear v. American Bell Telephone Co.*, 126 U.S. 1 (1888); *U.S. v. American Bell Telephone Co.*, 128 U.S. 315 (1888); *In re Borkowski*, 164 USPQ 642 (CCPA 1970); *In re Strahilevitz*, 212 USPQ 561 (CCPA 1982).

Applicants respectfully submit that the Office has not established a *prima facie* case of non-enablement. In view of the success in treating liver tumors *in vivo*, which was presented in the October 26, 2007 Declaration, the Action has not provided any reasons as to why it will not be predictable to use the p19ARF 26-44 peptide to treat other types of tumors. The specification is not required to contain evidence of actual reduction to practice, much less actual reduction to practice in *every tumor model*. The Action merely conclusorily states that the art of treating cancer is highly unpredictable and thus requires more guidance. The Action, however, does not explain why it is unpredictable to use the peptide to inhibit different proliferating tumor cells that express the important proliferation factor FoxM1B by inhibiting FoxM1B, particularly in the face of evidence that liver tumor cells are inhibited from proliferating using the p19ARF 26-44 peptide. Applicants respectfully submit that the Office has failed to "substantiate its rejection for lack of enablement with *reasons*." See *In re Armbruster*, 185 USPQ at 153.

Notwithstanding the Office's failure to establish a *prima facie* case of non-enablement, Applicants have amended the claims and submit that the currently pending claims are fully enabled. Claim 1 as amended is directed to a method of inhibiting proliferation of a tumor cell comprising the step of inhibiting FoxM1B activity in the tumor cell by contacting the cell with a p19ARF protein fragment, wherein the p19ARF protein fragment has the amino acid sequence as set forth in SEQ ID NO:10, and wherein the tumor cell expresses FoxM1B protein.

One of the points of novelty of the current invention is the discovery that the claimed p19ARF peptide binds to and inhibits the activity of FoxM1B, which has been demonstrated to play a pivotal role in tumor cell proliferation. Co-inventor Dr. I-Ching Wang now testifies in the attached Declaration (the "Declaration") that FoxM1B is expressed in a variety of tumor cells, not just liver tumor cells, and that the p19ARF peptide may have broad therapeutic benefits in treating different types of cancers. Thus, one of skill in the art would have been able to, at the time of the invention, use the peptide to treat different types of tumors without undue experimentation.

In his Declaration, Dr. Wang attests that FoxM1 B is expressed in various tumor cells of different origins, such as hepatocellular carcinoma cells, pancreatic neuroendocrine tumor cells, as well as osteosarcoma cells. See Declaration, paragraph 7. Dr. Wang further attests that FoxM1B is expressed in tumor cells of epithelial as well as mesoderm origin. *Id.* He also attests that FoxM1B expression was detected at elevated levels in a variety of different tumors including kidney tumors, breast cancers, prostate cancers, colonic adenocarcinomas, intrahepatic cholangiocarcinomas, basal cell carcinomas, ductal breast carcinomas, anaplastic astrocytomas, glioblastomas, and non-small cell lung cancers, in addition to hepatocellular carcinoma. See paragraph 8 of the Declaration.

Dr. Wang further avers that the p19ARF peptide inhibited FoxM1B activities not only in liver tumor cells, but in a variety of cell types, including osteosarcoma cells, endothelial cells, and adenocarcinoma cells. See paragraph 9 of the Declaration. He then concludes that the evidence establishes that FoxM1B is expressed in many proliferating tumor cells of diverse origins, including but not limited to tumor cells of epithelial origin, and that FoxM1B plays a pivotal role in tumor cell proliferation. He further concludes that the p19ARF 26-44 peptide is capable of inhibiting FoxM1B in a variety of cells, not just liver tumors or tumor cells of epithelial origin. Thus, Dr. Wang opines that the evidence of record would be sufficient to

convince someone knowledgeable in the field of oncology that p19ARF peptide would have broad therapeutic benefits in treating different types of tumors that express FoxM1B at elevated levels. See paragraph 10 of the Declaration.

Based on the evidence presented above and Applicants' arguments already on record, Applicants submit that the specification sufficiently enables one of skill in the art to make and use the full scope of the claimed invention. The specification not only teaches how to make the claimed peptide, it also teaches how to use the p19ARF peptide to inhibit tumor cell growth *in vitro*. See page 6 of Applicants' Response submitted October 26, 2007. Further, Applicants have established, and the Action does not dispute otherwise, that the specification enables how to use the peptide to inhibit liver tumor cell growth *in vivo*. See the October 26, 2007 Declaration. Dr. Wang now has testified in the Declaration submitted herewith that FoxM1B is commonly expressed in a variety of tumors, not just liver tumors. He has further testified that the inhibitory effects of the p19ARF peptide on FoxM1B were observed in different tumor cells that express FoxM1B, not just in liver tumor cells. Some of the research results cited in the Declaration were published after the filing date of the instant application; however, Applicants submit that because FoxM1B is commonly expressed in different types of tumor cells, one of skill in the art would have been able to successfully treat different types of tumors that express FoxM1B using the peptide, merely by practicing the invention as disclosed in their specification. Thus, one of skill in the art would have been able to, at the time of invention, practice the claimed method to its full scope without undue experimentation. The after-filing evidence simply confirms what Applicants had already taught the art in their specification: that FoxM1B was expressed in a variety of proliferating cell types, particularly tumor cells.

Based on the foregoing, Applicants respectfully submit that the enablement requirement has been fully met. Reconsideration and withdrawal of the rejection under 35 USC 112, first paragraph is thus respectfully requested.

III. Conclusions

Applicants respectfully submit that all conditions of patentability are satisfied in the pending claims. Allowance of the claims is thereby respectfully solicited.

The Examiner in charge of this application is invited to contact the undersigned representative as indicated below if it is believed to be helpful.

Respectfully submitted,

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